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Sex Hormone Levels by Presence and Severity of Cirrhosis in Women With Chronic Hepatitis C Virus (HCV) Infection

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Abstract

Cirrhosis is associated with hormonal dysregulation, as evidenced by secondary amenorrhea in reproductive-aged women, and feminization of cirrhotic men. Whether hormone levels vary by severity of cirrhosis in women is not known. If identified, such changes may have important clinical relevance, particularly as low sex hormone binding globulin (SHBG) and follicle stimulating hormone (FSH) are known to promote metabolic and cardiovascular disease in women. In a cohort of post-menopausal women with chronic hepatitis C virus (HCV) infection, we compared comprehensive sex hormone levels by presence of cirrhosis, as well as across Child-Turcotte-Pugh (CTP) class.

Results: There were n=18 cirrhotic and n=21 non-cirrhotic women with a median age of 57 years (interquartile range, IQR 53–62). Compared to non-cirrhotics, cirrhotic women had higher estradiol (11.0 vs 6.0 pg/ml, $p = 0.05$) and estrone levels (32.0 vs 8.0 ng/ml, $p < 0.001$), and lower sex hormone binding globulin (SHBG) (69.2 vs 155.6 nmol/L, $p=0.001$), and follicle stimulating hormone (FSH) levels (4.9 vs 89.6 mIU/ml, $p<0.001$). Among cirrhotic women there was a progressive decline in FSH and SHBG, and concurrent rise in estrone levels from CTP class A to C (test of trend, p values ≤0.02) Cirrhosis is associated with lower FSH and SHBG levels in cirrhotic compared to non-cirrhotic women with HCV infection. In cirrhotic women, these levels demonstrate steady decline by disease severity. Given known associations of low SHBG and FSH

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with cardio-metabolic disease, the clinical implications of hormonal changes by cirrhosis severity in HCV-infected women warrants investigation.

Keywords

Hormones; liver disease; hepatitis C; women; fibrosis

Introduction:

End-stage liver disease is known to cause hormonal dysregulation in both men and women. Reproductive-aged women with cirrhosis typically have secondary amenorrhea(1), while peripheral conversion of androgens to estrogens and increase in sex hormone binding globulin (SHBG) levels, contributes to feminization of cirrhotic men.(2) A single study in men with chronic hepatitis B infection also found lower testosterone and follicle stimulating hormone (FSH) levels, as well as higher estrone levels in those with cirrhosis compared to non-cirrhotic controls.(3) These changes were modified by severity of liver disease, with the most profound changes among men with greater severity of liver dysfunction. In healthy women, menopause normally leads to declining estradiol levels and rise in FSH, which are associated with risk of cardiac(4) and bone disease(5), respectively. Less is known about the effect of cirrhosis on sex hormone production and metabolism in post-menopausal women, including whether hormone levels vary by severity of cirrhosis resulting from chronic hepatitis C virus (HCV) infection.

In order to address existing knowledge gaps, we aimed to compare levels of a comprehensive panel of sex hormones in post-menopausal women by cirrhosis status, as well as across severity of cirrhosis as defined by Child-Turcotte-Pugh (CTP) class. Given established associations of altered sex hormones and various metabolic conditions, such findings could have relevant clinical implications for the long-term health of post-menopausal cirrhotic women.

Methods:

Study Design and Study Patients:

We conducted a cross sectional study of post-menopausal women with chronic HCV infection, conducted at two study sites, the University of California, San Francisco and the University of Pennsylvania. Socio-demographics, medical comorbidities and medications, HCV-related history, menstrual history and substance use was obtained by patient questionnaires and/or chart review. Serum laboratory data, including albumin, international normalized ratio (INR), sodium, and total bilirubin were obtained within 6 months of fibrosis assessment. Chronic HCV infection was confirmed by at least two detectable HCV viral load measurements, at least 6 months apart prior to study enrollment. Viral load was measured using Real-Time PCR at clinical laboratories guided by patient insurance, with a lower limit of HCV detection of 15 IU/ml. Menopausal status was determined by self-report at the time of study enrollment. Cirrhosis was confirmed by histology in all but one woman who was determined to be cirrhotic by a nodular appearing liver and splenomegaly on imaging and concurrent thrombocytopenia. Absence of cirrhosis was defined as stages 1–3

on biopsy or the combination of the following three criteria: (a) Platelet count > / = 140,000 per uL (b) Absence of complications of end-stage liver disease (e.g., varices, ascites, or hepatic encephalopathy), and (c) Lack of imaging evidence of cirrhosis or portal hypertension (nodular liver edge, splenomegaly, enlarged portal vein or intra-abdominal collaterals). Severity of cirrhosis was categorized by Child-Turcotte-Pugh (CTP) class.(6) Study participants underwent banking of blood within 6 months of fibrosis assessment. These specimens were used for sex hormone measurements as noted below.

Sex Hormone Assays

Sex hormone assays in duplicate batches were performed at the laboratory of the Wisconsin National Primate Research Center. Estradiol, estrone, dehydroepiandrosterone sulfate (DHEAS), androstendione, total testosterone, and progesterone were measured by a multi-steroid liquid chromatography tandem mass spectrometry (LC/MS/MS) method.(7) FSH and SHBG were measured using commercial enzyme-linked immunosorbent assay (ELISA). Four women with prior oophorectomy were excluded from analyses of all sex hormones except for estrone, DHEAS, and SHBG, as oophorectomy is not anticipated to affect these three hormone levels. There were an additional two women with exogenous estradiol use that were excluded from analyses of estradiol, estrone, SHBG and FSH levels given potential effect of exogenous estradiol use on these specific hormone levels. Interassay coefficient of variation was 3.7% for estradiol, 8.7% for estrone, 11.2% for DHEAS,10.8% for androstendione, 9.9% for testosterone, 6.1% for progesterone, 12.6% for FSH and 4.6% for SHBG.

Statistical Analysis:

Categorical variables were summarized by frequencies and proportions, and continuous variables summarized by medians and interquartile ranges (IQR). For the primary analysis, hormone levels in women with and without cirrhosis were compared. Categorical variables were compared using a chi-squared test or Fisher’s exact test. Continuous variables were compared using a Student’s t-test or Wilcoxon rank sum test, as appropriate. Additionally, sex hormone levels were compared by CTP class. Continuous variables were compared by Kruskal-Wallis tests, as well as tests of trend. Statistical significance was considered at a p-value < 0.05. Analyses were performed using Stata version 12.1 (StataCorp, College Park, TX). Approval was obtained from the institutional review boards at the two study sites. Informed consent was obtained from all patients to be included in this study.

Results:

The study cohort included 18 cirrhotic and 21 non-cirrhotic women with chronic HCV infection. The median age was 57 years (IQR 53–62); 61% were white, 27% black, and 12% Hispanic with similar age and race/ethnicity by cirrhosis status (p values ≥ 0.40). There were no cirrhotic patients with current alcohol use, and among the 6 non-cirrhotic women reporting current use, all consumed ≤ 2 alcoholic drinks per day.

Estrogen levels were higher in cirrhotic compared to non-cirrhotic women, including higher median estradiol levels (11.0 ng/ml, IQR 4.0–31 vs 6.0 ng/ml, IQR 0.0–0.9, p=0.054) and

higher estrone levels (32.0 ng/dL IQR, 22.0–70.0 vs 8.0 ng/dL, IQR 4.0–14.0, p<0.001) (Table 1). Compared to non-cirrhotics, HCV infected cirrhotic women had lower median DHEAS levels (4.4 mcg/dL, IQR 1.8–24.8 vs 40.4 mcg/dL,IQR 13.1–65.7, p=0.013) and lower progesterone (0.05 ng/ml, IQR 0.04–0.60 vs 4.2 ng/ml, IQR 0–6.3, p=0.140) though progesterone comparison did not reach statistical significance. Androstendione and testosterone levels were similar by cirrhosis status (p values ≥ 0.26). Cirrhotic women had markedly lower FSH levels (4.9 mIU/ml, IQR 4.0–51.5 vs 86.5 mIU/ml, IQR 64.7–145.8 p<0.001). FSH levels in cirrhotic women also reflected lower than expected ranges as compared to healthy post-menopausal controls.(8) Median SHBG levels were also lower in cirrhotic than non-cirrhotic women (69.2 nmol/L, IQR 44.9–112.3 vs 155.6 nmol/L, IQR 101.2–178.0, p=0.001).

Regarding severity of cirrhosis, estrone levels were higher in women with CTP class C (p=0.091) compared to CTP classes A and B (test of trend p values ≤ 0.029) (Table 1). Both SHBG (p=0.062) and FSH (p=0.021) levels demonstrated progressive decline with increasing severity of liver disease, with test of trend p values of 0.037 and 0.005, respectively. The remainder of hormone levels were similar by CTP class (p values ≥ 0.40).

Discussion:

In the current study, we identified changes in a comprehensive panel of sex hormones, not only by presence of cirrhosis, but also across severity of cirrhosis as defined by CTP class. Notably, estrogen levels, including estradiol and estrone, were higher in cirrhotic women, while FSH and SHBG levels were conversely lower. These changes were pronounced across severity of liver disease with rising estrone levels as well as declining SHBG and FSH with increasing CTP class.

The clinical implications of the current findings warrant further investigation. Estrogens are known for their cardio-protective effects, although it is not known whether higher estrogen levels in the context of cirrhosis confer any decrease in cardiovascular risk. Importantly, low SHBG has been associated with increased risk of dyslipidemia, insulin resistance, and diabetes mellitus in post-menopausal women, independent of estrogen levels.(9, 10) Low SHBG has also been shown to be associated with risk of nonalcoholic fatty liver disease (NAFLD) in post-menopausal women, regardless of estrogen levels.(11, 12) This association may relate to the direct SHBG effect on hepatic lipogenic enzyme activity.(11, 12) Whether low SHBG may also be a marker of metabolic risk in individuals with cirrhosis is not known.

Like SHBG, low FSH levels are also associated with obesity, diabetes mellitus, as well as risk of NAFLD in post-menopausal women, largely independent of estrogen levels.(13, 14) Recent data specifically highlight the association of low FSH on risk of CAD in post-menopausal women, which may relate to the pro-angiogenic activity of FSH.(15) We also identified lower DHEAS in cirrhotic women, a finding which has been observed in other forms of advanced liver, such as advanced NASH fibrosis.(16) Interestingly, in women with hypoadrenalism, DHEA replacement has been shown to improve insulin sensitivity, suggesting its potential contribution to glucose homeostasis and cardio-metabolic health.(17)

The reasons for altered sex hormones in cirrhosis is complex, and includes impairment at the level of the hypothalamus, with decreased levels of gonadotropin releasing hormone, as well as impaired release of FSH and luteinizing hormone from the anterior pituitary.(18, 19) Despite the presence of hypogonadotropic hypogonadism, higher circulating levels of estradiol are evident in cirrhosis, due primarily to increased peripheral conversion of androgens to estrogens.(20, 21). Prior data from male predominant cohorts do note higher levels of SHBG in patients with cirrhosis, as compared to healthy controls(22), which may also contribute to feminization of cirrhotic men. In contrast, we observed lower SHBG levels by presence and severity of cirrhosis which likely reflects differences in study population, as the current analysis compares SHBG levels within a post-menopausal population, all of whom had chronic HCV infection. Similar to our study, lower SHBG levels have been observed in men with decompensated as compared to compensated cirrhosis from non-alcoholic causes of liver disease (22), suggestive of impaired hepatic production of SHBG, with more severe liver disease.

The observed changes in sex hormones in cirrhotic women may have unique implications in the context of liver transplant. A growing number of cirrhotic patients now achieve HCV cure, and may avoid liver transplant due to improvement and/or stability of liver function. This population will be living longer with cirrhosis, and hence at risk for morbidity and mortality related to metabolic disease. CAD in particular has traditionally been thought to be lower risk in cirrhotics due to their favorable lipid profiles and lower platelet count, though emerging data suggest similar CAD risk as non-cirrhotic controls.(23) Within the post liver transplant population, CAD remains a leading cause of death.(24) CAD risk is compounded by immunosuppression-related side effects, such as dyslipidemia and insulin resistance, and post-transplant weight gain (25), with an emerging epidemic of de novo NAFLD after transplant.(26, 27) Whether an adverse hormonal profile during the pre-transplant cirrhotic years could set the stage for post-transplant metabolic disease warrants investigation.

There were notable strengths and limitations of the current study. Despite the small sample size, statistically significant differences in sex hormone levels by cirrhosis status were nonetheless identified. However, larger subgroups of women within each CTP class, would have allowed for more robust comparisons of hormone measures. Given the cross-sectional nature of our study, we did not evaluate how the observed changes in hormone levels may affect the development of subsequent metabolic co-morbidities. However, the current findings support the need for future studies evaluating metabolic disease in women with liver disease to consider sex hormone levels.

In summary, we identified changes in sex hormone profiles between cirrhotic and non-cirrhotic women with chronic HCV infection. There were higher estrogen levels, as well as lower SHBG and FSH levels by both presence and severity of cirrhosis. These findings may have important clinical implications, particularly in light of established associations of low FSH and SHBG with metabolic co-morbidities in post-menopausal women. With a growing population achieving HCV cure, sex hormones should be considered in our efforts to identify and optimize the long-term health of women with advanced HCV fibrosis.

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Table 1.

Sex Hormone Levels in Post-menopausal Women with Chronic Hepatitis C Infection by Presence and Severity of Cirrhosis

Measure[t]	Reference range[*]	Cirrhotic (n=18)	Non-Cirrhotic (n=21)	p value
Age (years)	-----	60 (52–64)	57 (54–59)	0.230
Estradiol (pg/ml)	<10.0	11.0 (4–31)	6.0 (0.0–9)	0.054
Estrone (pg/ml)	7–40	32.0 (22.0–70)	8.0 (4.0–14.0)	<0.001
DHEAS (mcg/dL)	<15–200	4.4 (1.8–24.8)	40.4 (13.1–65.7)	0.013
Androstendione (ng/dL)	30–200	66.7 (40.8–108)	49.8 (37.5–75.5)	0.260
Total testosterone (ng/dL)	8.0–60	33.8 (20.5–263)	29.0 (24.9–333)	0.289
Progesterone (ng/ml)	≤ 0.20	0.05 (0.04–0.60)	4.2 (0–6.3)	0.144
FSH (mIU/ml)	16.7–113.6	4.9 (4.0–51.5)	86.6 (64.7–145.8)	<0.001
SHBG (nmol/L)	18–144	69.2 (44.9–112.3)	155.6 (101.2–178.0)	0.001
	Child-Turcotte-Pugh (CTP) Class			
Measure[t]	**CTP A (n=3)**	**CTP B (n=9)**	**CTP C (n=6)**	**p value[**]**
Estrone (pg/ml)	23.0 (7.0–30.0)	28.0 (19.0–107)	58.0 (38.0–70)	0.091
FSH (mIU/ml)	67.6 (10.7–125.2)	5.1 (4.0–51.8)	3.3 (1.9–4.6)	0.021
SHBG (nmol/L)	171.0 (81.8–177.1)	89.7 (48.1–104.3)	43.6 (32.3–56.7)	0.062

[t] Estimates reflect median (interquartile range)

[*] https://www.mayomedicallaboratories.com, reflects 90th percentile for healthy post-menopausal women, except for total testosterone which reflects 90th percentile for healthy women ≥ 19 years of age.

[**] Test of trend p values ≤ 0.02 for all comparisons